REMARKS/ARGUMENTS

Claims 1-5, 7-27, and 29-34 are pending in the above-identified application. No claims have been amended in the current response. The Examiner is requested to reconsider the below rejections in view of the remarks below.

Rejections Under 35 U.S.C. §112:

Claims 5 and 15 remain rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record.

As previously stated Applicants will provide a Declaration assuring public availability of the deposited material when allowable subject matter has been indicated. It is understood that the present rejection will be maintained until the assurance is obtained.

Rejections Under 35 U.S.C. § 103

Claims 1-4, 7-14 and 16-34 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Midthun *et al.* (*J. Virol.* 53:949-954, 1985; designated herein as Midthun '85), Midthun *et al.* (*J. Clin. Microbiol.* 24:822-826, 1986; designated herein as Midthun '86), Hoshino *et al.* (*J. Med. Virol.* 51:319-325, 1997), Clark *et al.* (US. Patent No. 6,113,910; designated herein as Clark *et al.*) and Clark *et al.* (*J. Infect. Dis.* 161:1099-104, 1990; designated herein as Clark *et al.* 1990).

The Examiner has summarized the pending claims being primarily drawn to a multivalent immunogenic composition comprising at least four bovine strain reassortant rotaviruses and a physiologically acceptable carrier, wherein each bovine reassortant rotavirus comprises a single rotavirus VP7 gene that encodes a protein that is immunologically cross-reactive with an antigenically distinct human VP7 serotype and the remaining 10 genes derived

from the bovine UK strain, and wherein the composition induces an effective immunogenic response to each antigenically distinct human rotavirus VP7 serotype without causing a transient low level fever in a statistically significant number of vaccinees when each of the rotavirus reassortant serotype is administered at a dosage of less than $10^{6.0}$ plaque forming units.

The Examiner has not specifically summarized or addressed claims 22 through 34 as being directed to a method for stimulating the immune system of an infant of less than six months of age to produce an effective immunogenic response to human rotavirus VP7 serotype antigen without significant transient low level fever in a statistically significant number of vaccinees.

Midthun *et al.* '85 and '86 are alleged by the Examiner to teach four human x bovine reassortant rotaviruses, where the reassortants have one human gene (D (serotype 1), DS-1(serotype 2), P (serotype 3) and ST3 (serotype 4)) from a human rotavirus serotype and where the bovine parent/backbone, which is the UK strain, provides the remaining 10 genes. Midthun *et al.* '85 and Midthun *et al.* '86 are acknowledged by the Examiner not to teach a multivalent immunogenic composition of four reassortant rotaviruses, a physiologically acceptable carrier, nor to teach the induction of an immunogenic response without causing a low level fever, or a dosage.

Clark *et al.*, is alleged by the Examiner to teach combining different human x bovine reassortant rotaviruses into a single composition. Clark *et al.* is also alleged to teach suitable carriers, liquid dose forms, buffers, lyophilized forms, adjuvants, multiple administrations, and methods for stimulating the immune system. Clark *et al.* is further alleged by the Examiner to teach a general dose range between 10^6 and 10^9 and other dosages of $10^{5.5}$, $10^{6.5}$ and $10^{7.5}$.

Clark *et al.* 1990 is alleged by the Examiner to disclose the safety and protective efficacy of a serotype 1 reassortant of bovine rotavirus, which contains a gene segment 9 coding for the surface structural protein VP7 of a human serotype 1 rotavirus, with all other gene

segments derived from WC3 rotavirus, which had previously been shown to be safe and immunogenic in infants. The Examiner has cited to portions of Clark *et al.* that allegedly describe the administration to infants 2-11 months of age two doses of vaccine ($10^{7.3}$ plaque-forming units/dose) or of placebo 28 days apart.

Hoshino *et al.* is alleged by the Examiner to teach that the four human serotypes (serotypes 1-4, also disclosed in Midthun *et al.* '85 and '86) are the most epidemiologically important serotypes.

Combining these alleged teaching the Examiner has concluded that it would have been obvious to one of ordinary skill in the art to modify the teachings of Midthun *et al.* '85 and '86 to produce a multivalent composition with two, three, four, five, six, *etc.*, reassortants and that one would have been motivated to do so given the numerous teachings of Clark *et al.*, in particular, the teaching to produce a multivalent composition of reassortants, to include more than one reassortant to elicit a stronger immune response, and to further combine the teachings of Hoshino *et al.* The Examiner has alleged that there would have been a reasonable expectation of success given the fact that it is common and routine to produce multivalent vaccines and given the knowledge that Clark *et al.* successfully vaccinated subjects with reassortant vaccines and also given the knowledge that WC3 strain of Clark *et al.* and the UK strain are of the same serotype (serotype 6). Finally, the Examiner alleges that the prior art references, when combined, teach or suggest all the claim limitations. Thus, the Examiner has concluded that the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicants must again strongly disagree with the Examiner's rejection. It is not disputed that there is motivation to combine animal rotavirus x human VP7 serotype rotavirus to form prospective vaccine compositions given that it was well known that the VP7 G1 through G4 serotypes were epidemiologically most important. But, the Examiner has alleged that there would be a reasonable expectation of success in producing a multivalent composition with two,

three, four, five, six, *etc.* reassortants in producing a multivalent vaccine that would induce an effective immunogenic response to each antigenically distinct human rotavirus VP7 serotype in infants of less than six months of age without causing a transient low level fever in a statistically significant number of vaccinees. In particular, the Examiner alleges that it would be obvious because Clark *et al.* successfully vaccinated subjects with reassortant vaccines and that it was common knowledge that the WC3 strain of Clark *et al.* and the UK strain of the present invention are the same serotype (serotype 6).

On the contrary Clark *et al.* only successfully vaccinated subjects with bovine WC3 x human VP7 G1 serotype rotavirus at an effective concentration of over 10^7 pfu. Applicants previously addressed this issue in the last response, but the Examiner has not provided a response to those arguments.

As presented previously there is no reason to believe that the bovine rotavirus strain WC3 and the bovine rotavirus strain UK would induce the same or similar immune response when administered to an individual, whether the individual were an adult, a child or an infant. The Examiner has alleged that the rotaviruses will induce a similar immune response because the two strains are VP7 serotype 6. The VP7 characterization system is an immunological based system wherein cross reactivity with the VP7 protein of the rotavirus separates the rotavirus into groups. In the reassortant rotavirus either the bovine VP7 or the VP4 protein is replaced with the corresponding human VP7 or VP4 protein. The Examiner has not provided any evidence that the VP7 or VP4 serologic characterization systems correlate with the ability of a bovine or human rotavirus to grow in an infected host or correlates with the ability of the rotavirus to induce an immune response.

Further, the Examiner has asserted that the UK and WC3 strains of rotavirus will demonstrate the same ability to induce an immunological response because they are both VP7 serotype 6. Applicants must point out that the VP7 gene from both the bovine UK and the bovine WC3 strains are removed in the production of the human x bovine reassortants. As such,

the factor associated by the Examiner with providing the necessary link between the two bovine rotaviruses and their ability to produce the same or similar immune response does not exist. Applicants believe the Examiner has not met the burden for stating a *prima facie* case for obviousness. In addition, as stated in paragraph 6 of the Kapikian Declaration filed with Applicants' response dated June 29, 2005, "[o]ur experience with human x rhesus rotavirus reassortants and with other non-human animal rotavirus and human x non-human animal rotavirus reassortants has relied on that principle that for exactly the reasons listed by the Examiner above, it is not possible to predict ahead of time whether any particular rotavirus composition will be sufficiently attenuated so as not to cause disease in human vaccinees and still retain sufficient immunogenicity to be effective in inducing an immune response capable of protecting against rotaviral disease'. As such, although Clark *et al.* may have demonstrated an effective bovine WC3 x human VP3, VP7 G1 composition at a dosage of greater than 10^6 pfu, the characterization of the bovine rotavirus strain WC3 and UK as VP7 serotype 6 provides no information to the skilled artisan relating to the ability of the parental rotavirus or a reassortant rotavirus comprising either WC3 or UK to induce an effective immune response at any dosage, much less at a dosage of less than 10^6 pfu. It is well known to a skilled artisan in the rotavirus art that any prospective vaccine composition must be empirically tested in adults, young children, and then infants to demonstrate with any reasonable expectation the ability of the composition to induce an effective immune response, much less the minimum dosage of the prospective composition necessary for inducing an effective immune response. Applicants direct the Examiner to paragraph 6, lines 24-31, wherein Dr. Kapikian states "[i]n the present case, the prior bovine rotavirus and human x bovine rotavirus reassortants were found to be highly attenuated in humans, typically requiring greater than 10^7 to 10^8, or more, plaque forming units of virus to obtain an effective immunogenic response in vaccinnees. By extrapolation from the prior art it might be anticipated that the human x bovine UK reassortant compositions of the present invention would not be capable of inducing an acceptable immune response to each antigenically distinct human rotavirus VP7 serotype included in the composition in a meaningful number of vaccinees at a concentration of less than 10^6 pfu."

The Examiner has further alleged that as for the number of components in the vaccine composition and dosages claimed, it is well within the purview of one of ordinary skill in the vaccine art to optimize dosages recited in the claims. Section 2144.05 of the MPEP, has been cited by the Examiner for the proposition that differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical.

Applicants disagree with the Examiner that the present invention is merely the optimization of a dosage. In *In re Peterson* cited by the Examiner, the Court held that a *prima facie* case of obviousness can be overcome by providing a showing that the critical characteristic resulted in an unexpected result. In the present case, methods for testing rotavirus vaccine compositions is generally known in the art. Typically, a prospective rotavirus vaccine composition is tested first in adults and young children to determine safety prior to testing for efficacy in infants. The prospective rotavirus vaccine composition is also typically tested at a number of different dosages. In the present case, Clark *et al.* merely demonstrate that the bovine WC3 reassortant rotavirus composition was effective in infants of 2 to 11 months at a dosage of $10^{7.3}$ pfu. As above no prediction can be made as to efficacy of a rotavirus vaccine composition in infants 6 months of age and younger even after safety and efficacy of the composition in adults or in young children has been demonstrated. (See paragraph 6 of the Kapikian Declaration). In particular, the amount of attenuation and immunogenicity for a particular prospective vaccine composition can not be predicted. The lack of predictability partially lies in the fact that infants of 6 months of age and younger have maternal anti rotavirus antibodies that can affect the ability of the live rotavirus composition to grow in the infant and to induce an effective immune response.

In addition, Clark *et al.* do not disclose a bovine reassortant composition wherein each reassortant rotavirus comprises only a VP7 antigen immunologically cross-reactive with a human VP7 serotype and the remaining genes from a bovine rotavirus at a dosage of less than 10^6 pfu that is effective inducing an immune response in an infant of less than 6 months of age.

Example 4 cited by the Examiner discloses a reassortant vaccine composition that consists of a human bovine reassortant wherein the VP3 and VP7 genes from a G1 serotype human rotavirus and the remaining genes are from the bovine rotavirus strain WC3. See, column 4, lines 42-53, Table 1 at column 5, subscript *a*, and column 10, lines 49-57. Further, as noted previously, Clark *et al.* disclose that the composition was administered at various concentrations, recited as $10^{5.5}$, $10^{6.5}$, and $10^{7.5}$ pfu to children of various ages. In Example 4 at column 12, lines 58 - 64, Clark *et al.* state "30 of 54 infants, or 57%, given any dose of vaccine developed a virus-neutralizing serum antibody response to one or more of rotavirus serotypes G1, G3 or bovine." As such, Clark *et al.* disclose that 57% of all infants administered the vaccine had neutralizing antibody to any of WC3, WI79, or SA11 (a human rotavirus stain of VP7 serotype 3). No data is provided that indicates whether any of the vaccinees that received the dosage of $10^{5.5}$ had developed neutralizing antibody, nor does the example provide any information relating to the age of the infants that received this dosage of vaccine. As such, Clark provides no disclosure that supports the use of a single gene substitution, *e.g.*, VP7, in a bovine rotavirus background. Further, the statement cited by the Examiner merely says that 57% of the vaccinees that received a dose of the composition at some concentration developed a virus-neutralizing serum antibody response to a rotavirus antigen. The tested antigens were G1, G3 and WC3 bovine. The skilled artisan can draw no reasonable conclusion about the effectiveness of the administration of specifically the $10^{5.5}$ dosage amount. Review of the remainder of the reference provides the skilled artisan with the teachings that the general dosage for a vaccine composition is from 10^6 to 10^9 and the remainder of the studies used a dosage of greater than 10^7 pfu.

Applicants must again direct the Examiner to the previously submitted reference, Clark *et al. Vaccine* 8:327-332, 1990. This reference has not been specifically addressed by the Examiner in any office action. The reference is cited in the Clark *et al.* patent and discloses what appears to be the a study in the Clark *et al.* patent. In particular, Applicants previously referred the Examiner to the study described in Table 3 and the left column of page 329. In this study, two (2) children of 12 months of age were administered the vaccine composition WI79-9 (designated WI79-3,9 is the patent) at a dosage of $10^{5.5}$ pfu. As such, Clark *et al.* may not

disclose the administration of a vaccine of less than 10^6 pfu to an infant of less than 6 months of age. Applicants do not believe that any skilled artisan reviewing the Clark *et al.* references together would have a reasonable expectation regarding the effectiveness of a WC3 composition at a dosage of $10^{5.5}$ much less a composition comprising a human x bovine UK reassortant composition such as claimed in the present application.

The Examiner also believes that it would have been obvious for one of ordinary skill in the vaccine arts to administer the human x bovine reassortants to infants of less than six months of age in view of the teachings of Clark *et al.* (1990) (serotype 1 bovine rotavirus reassortant provided 100% protection for vaccinated infants age 2 - 11 months) and to use a citrate buffer. Applicants must again strongly disagree with the conclusion of the Examiner. In particular, the study in referred to in Clark *et al.* by the Examiner uses a WC3 bovine strain rotavirus x human VP7 G1 vaccine at a dosage of $10^{7.3}$ pfu. The results described can not be extrapolated to a human x bovine WC3 reassortant much less a composition comprising a human x bovine UK rotavirus reassortant. As to the use of a citrate buffer, the Examiner must first present a *prima facie* case that the composition of a bovine UK x human VP7 reassortant rotavirus was obvious before the use of a citrate buffer can be considered. Therefore as above, no reasonable prediction can be made regarding the efficacy of a vaccine composition consisting of a bovine UK strain x human reassortant vaccine composition used at a concentration of less than 10^6 pfu or the use of a citrate buffer in formulating the composition.

The Examiner has again asserted that the $10^{5.5}$ dose of Clark *et al.* was effective and provides a reasonable expectation of success for the $10^{5.5}$ dose and other doses of human x bovine reassortants, and furthermore, because the following trial in Example 5 of Clark *et al.* used a higher dose it does not indicate that the previous dose of $10^{5.5}$ was ineffective. Based on this conclusion the Examiner has asserted that the combined teachings of Midthun '85, Midthun '86, Clark *et al.* and Clark *et al.* 1990 teach the claimed invention (an immunogenic composition comprising at least four human x bovine (UK) reassortants) as outlined above.

As above, Applicants disagree with the reasoning of the Examiner. The statement cited by the Examiner in Clark *et al.* is no more than a general conclusion regarding all of the individuals vaccinated with the WC3 reassortant used in the Example. Applicants have also noted above that the reference does not provide any information regarding the age of the infants receiving the $10^{5.5}$ pfu dosage of vaccine. As such, the statement not only does not distinguish between the dosages that provided the immune response or the age of the vaccinees, but it also does not provide any information regarding the antigen to which the response is directed, G1, G3 or WC3. Also, the composition comprised a bovine WC3 strain rotavirus which does not provide the skilled artisan with any information regarding a composition comprising a bovine UK strain reassortant. In addition, Applicants have noted that the reassortant of Clark *et al.* was a double gene replacement having the VP3 and VP7 genes from a human rotavirus strain.

In order to clarify the statement in Clark *et al.*, Applicants previously provided Clark *et al.*, *Vaccine* 8:327-332, 1990. As above, this reference describes what appears to be the same study disclosed in Clark *et al.* The description in the reference clarifies that the WI79-9 (designated WI79-3,9 in Clark *et al.*) was administered at a dosage of $10^{5.5}$ pfu to two children of 12 months of age not infants of less than six months of age as claimed in the present application. The skilled artisan can make no reasonable conclusion as to the effectiveness of a UK bovine x human reassortant when used at a dosage of less than 10^6 pfu based on the combination of Clark *et al.* and the Clark *et al. Vaccine* reference.

The Examiner also found Applicants' prior arguments that the Midthun *et al.* references add nothing to the teaching of Clark *et al.* to suggest that a human x bovine UK reassortant could have been successfully used at a dosage of less than 10^6. The Examiner has responded by alleging that it is well known that the WC3 strain of Clark *et al.* and the UK strain are of the same serotype citing, for example, Gouvea *et al.* (*J. Clin. Microbiol.* 32:1338-1340, 1994) and that therefore, it is reasonable for one of ordinary skill in the art to believe that the UK strain used in Midthun '85 and '86 would behave similarly. Further, the Examiner alleges that the statements from Midthun *et al.* '85 "[t]he single human rotavirus gene substitution

reassortants described in this study represent potential vaccine candidates. The major neutralization protein of these reassortants is derived from the human rotavirus parent, and these viruses should therefore have the desired immunogenicity. It is also likely that the presence of 10 animal rotavirus genes in these reassortants will render such viruses attenuated for humans. This latter supposition is supported by the fact that bovine rotavirus UK and RRV have been administered to susceptible volunteers with a low level of serum antibodies and did not produce illness (Kapikian *et al.*, in press; Wyatt *et al.*, in press). These findings suggest that single human rotavirus gene substitution reassortants may be promising vaccine candidates for use in prevention of human rotavirus disease." Emphasis added. From this statement the Examiner alleges that because the reassortants described in the Midthun *et al.* studies were based on the UK strain it is reasonable to believe that the UK strain will be successfully used in human x bovine reassortants at a dosage of less than 10^6 in infants of less than 6 months of age as discussed above.

Applicants have reviewed the passage from Midthun *et al.* '85 cited by the Examiner and must again disagree with their interpretation. In particular, Applicants note that the support for the supposition is "the fact that bovine rotavirus UK and RRV have been administered to susceptible volunteers" refers to a safety study in adult volunteers. As such, the supposition is that the UK reassortants "will render such viruses attenuated for humans". There is no reasonable expectation to the skilled artisan that the composition is a vaccine composition that will be effective at inducing an immune response in infants less than 6 months of age at any dosage, much less a dosage of less than 10^6 pfu. The statement merely suggests that the compositions will be attenuated. One particular question that remains unanswered for the skilled artisan is whether to composition would be over attenuated and therefore unable to induce an immune response. The Examiner is directed to paragraph 6 of the Kapikian Declaration where the lack of extrapolation of evidence of attenuation in adults can be extended to infants. As such, Applicants believe that the dosage of the vaccine composition is a critical feature of the claimed invention and that the skilled artisan would have no reasonable expectation that a bovine UK x human rotavirus reassortant of the claimed invention would be capable of inducing an effective

immune response in infants of less than 6 months of age when administered at less than 10^6 pfu. Applicants believe that the Examiner has failed to establish a *prima facie* case for obviousness and respectfully request that the rejection of claims 1-4, 7-14 and 16-34 under 35 U.S.C. § 103(a) as being unpatentable over Midthun '85, Midthun '86, Hoshino *et al.*, Clark *et al.* and Clark *et al.* 1990.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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